Modification of the Skeleton of Homoharringtonine through Unusual Rearrangements

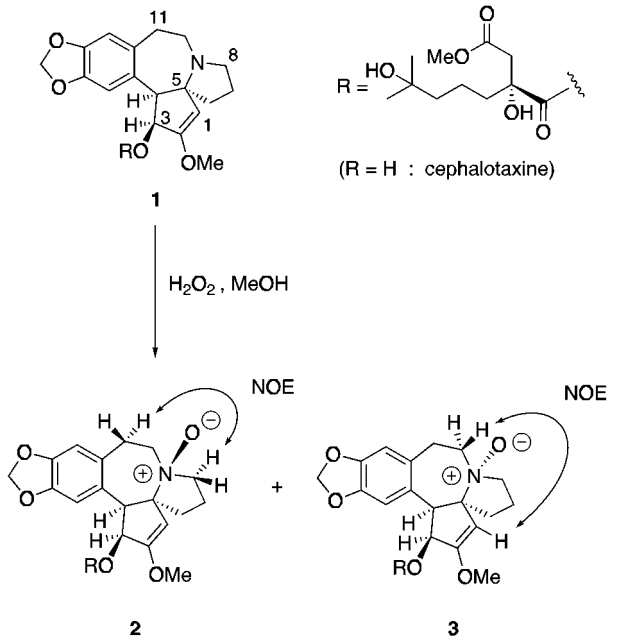
Ichiro Takano,*,† Ichiro Yasuda,† Motohiro Nishijima,† Yukio Hitotsuyanagi,‡ Koichi Takeya,‡ and Hideji Itokawa‡

The Tokyo Metropolitan Research Laboratory of Public Health, Hyakunin-cho, Shinjuku-ku, Tokyo 169, Japan, and Tokyo University of Pharmacy and Life Science, Horinouchi, Hachioji, Tokyo 192-03, Japan

Received June 26, 1997[⊗]

Homoharringtonine (**1**) is an antileukemic alkaloid isolated from *Cephalotaxus* plants.[1] Although alkaloid **1** is currently undergoing phase II clinical trials as an anticancer agent in the United States, its high toxicity hampers further clinical evaluation.[2] Despite its importance as a potential anticancer drug, little is known about the structure−activity relationships of this class of alkaloids.[3] We regarded that such information would be necessary for the rational approach toward designing an alternative to **1** possessing a more promising biological profile. Previous efforts toward the modification of these alkaloids addressed the substitution of the ester moiety by various acyl groups,[4] and a number of minor alkaloids possessing a different ester group have been isolated from these plants.[5] The evaluation indicated that this acyl part is very important for expressing the activity. To examine the influence of the cephalotaxine skeleton upon the activity, retention of this acyl moiety in the skeleton-modified analogues is requisite. Thus, we devised a method to produce analogues from homoharringtonine (**1**), the most abundant ester-type *Cephalotaxus* alkaloid showing potent antitumor activity. Since we suspected that the nitrogen lone pair may play an important role in expressing the activity, modification was done around this region.

Scheme 1



Oxidation of **1** with hydrogen peroxide in methanol gave *β*-*N*-oxide **2** and α-*N*-oxide **3** in 26% and 36% yields, respectively (Scheme 1). Their *N*-oxide configurations were assigned by observing the NOESY correlations between H-8α (δ_H 3.06, td, J = 10.0, 7.0 Hz) and H-11α (δ_H 2.74, m) for **2** and between H-1 (δ_H 4.92, s) and H-10*β* (δ_H 3.61, m) for **3**. When the 1,2-dimethoxyethane solution of *β*-*N*-oxide **2** was heated in a sealed tube at 105 °C for 2 h, compound **4** and unexpected compounds **5** and **6** were obtained in yields of 37%, 44%, and 7.7%, respectively (Scheme 2). Heating of α-*N*-oxide **3** under the same conditions also gave compounds **4** (32%), **5** (36%), and **6** (7.6%). The structures of these products were elucidated using spectroscopic methods. High-resolution FAB mass spectra showed that compounds **4**−**6** possess the same molecular formula as **2** and **3**. ^{1}H and ^{13}C NMR spectra showed that they retain an intact ester side chain, a methylenedioxy group, and a methyl enol ether moiety. Although the HMBC spectrum suggests that compound **4** possesses the same carbon framework as **1**, the low-field (δ_C 87.5) shift of the C-1 resonance in the ^{13}C NMR spectrum indicated that the oxygen atom is connected to this carbon. NOESY correlations were observed between H-2 (δ_H 4.97, s) and H-20*β* (δ_H 1.68, m) and between H-5 (δ_H 3.32, d, J = 7.2 Hz) and H-20α (δ_H 2.04, td, J = 12.8, 6.0 Hz). These observations led to the structure assignment as shown in **4**. This structure was supported by converting **4** into homoharringtonine (**1**) through zinc/acetic acid reduction (94% yield).

Compounds **5** and **6** showed similar ^{1}H and ^{13}C NMR spectra, the most characteristic feature being the presence of a doublet methyl signal (δ_H 1.83, J = 6.8 Hz for **5**; δ_H 1.71, J = 7.3 Hz for **6**). Analysis of the HMBC spectra gave the same carbon framework for **5** and **6**, and the ^{13}C NMR chemical shifts indicated that the oxygen atom is connected to C-1 (δ_C 89.0 for **5**; δ_C 84.7 for **6**) and the nitrogen atom to C-15 (δ_C 65.3; 71.5) and C-17 (δ_C 62.5; 72.0). Key NOESY correlations were observed between H-15 (δ_H 4.39, q, J = 6.8 Hz) and H-2 (δ_H 5.29,

* To whom correspondence should be addressed: The Tokyo Metropolitan Research Laboratory of Public Health, 3-24-1 Hyakunin-cho, Shinjuku-ku, Tokyo 169, Japan. Tel. 81-3-3363-3231. Fax. 81-3-3368-4060. E-mail. itakano@tokyo-eiken.go.jp.

† The Tokyo Metropolitan Research Laboratory of Public Health.

‡ Tokyo University of Pharmacy and Life Science.

⊗ Abstract published in *Advance ACS Abstracts*,October 15, 1997.

(1) (a) Powell, R. G.; Weisleder, D.; Smith, C. R., Jr.; Rohwedder, W. K. *Tetrahedron Lett.* **1970**, 815. (b) Powell, R. G.; Weisleder, D.; Smith, C. R., Jr. *J. Pharm. Sci.* **1972**, *61*, 1227. (c) Mikolajczak, K. L.; Powell, R. G.; Smith, C. R., Jr. *Tetrahedron* **1972**, *28*, 1995.

(2) NCI/PDQ Investigational Drug: Homoharringtonine, Updated 05/96, CancerNet from the National Cancer Institute, http://www.cyber.nl/cancernet/802110.html.

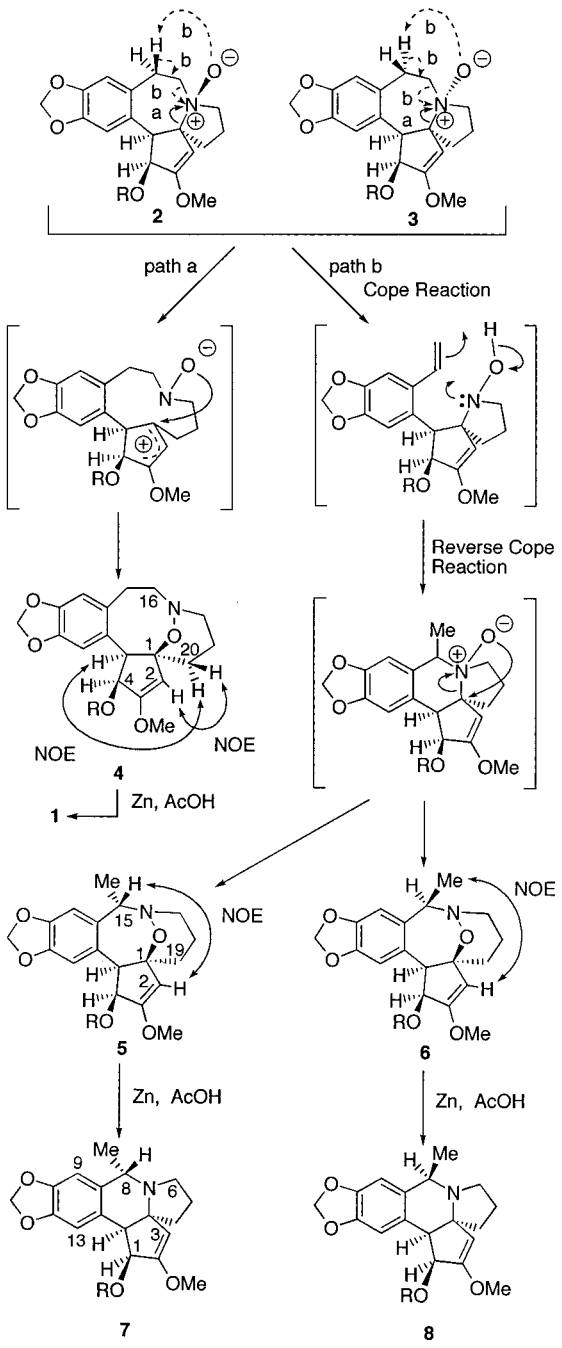
(3) Huang, L.; Xue, Z.; In *The Alkaloids*; Brossi, A., Ed.; Academic Press: Orlando, 1984; Vol. 23, pp 157−226.

(4) (a) Mikolajczak, K. L.; Smith, C. R., Jr.; Powell, R. G. *J. Pharm. Sci.* **1974**, *63*, 1280. (b) Li, S.; Dai, J. *Acta Chim. Sin.* **1975**, *33*, 75. (c) Mikolajczak, K. L.; Powell, R. G.; Smith, C. R., Jr. *J. Med. Chem.* **1975**, *18*, 63. (d) Mikolajczak, K. L.; Smith, C. R., Jr.; Weisleder, D. *J. Med. Chem.* **1977**, *20*, 328. (e) Li, S.; Sun, H.; Lu, X.; Zhang, S.; Lu, F.; Dai, J.; Xu, Y. *Acta Pharm. Sin.* **1981**, *16*, 821. (f) Mu, Q.; Li, Y.; Huang, W. *Kexue Tongbao* **1982**, *27*, 759. (g) Chan, C.; Huang, X.; Xiao, D.; Zhu, J.; Lu, L. *J. Hangzhou University, Sc. Ed.* **1983**, *10*, 87.

(5) (a) Wang, D. Z.; Ma, G. E.; Xu, R. S. *Acta Pharm. Sin.* **1992**, *27*, 173. (b) Wang, D. Z.; Ma, G. E.; Xu, R. S. *Acta Pharm. Sin.* **1992**, *27*, 178. (c) Takano, I.; Yasuda, I.; Nishijima, M.; Hitotsuyanagi, Y.; Takeya, K.; Itokawa, H. *Phytochemistry* **1996**, *43*, 299. (d) Takano, I.; Yasuda, I.; Nishijima, M.; Hitotsuyanagi, Y.; Takeya, K.; Itokawa, H. *J. Nat. Prod.* **1996**, *59*, 965. (e) Takano, I.; Yasuda, I.; Nishijima, M.; Hitotsuyanagi, Y.; Takeya, K.; Itokawa, H. *J. Nat. Prod.* **1996**, *59*, 1192. (f) Takano, I.; Yasuda, I.; Nishijima, M.; Hitotsuyanagi, Y.; Takeya, K.; Itokawa, H. *Bioorg. Med. Chem. Lett.* **1996**, *6*, 1689. (g) Takano, I.; Yasuda, I.; Nishijima, M.; Hitotsuyanagi, Y.; Takeya, K.; Itokawa, H. *Tetrahedron Lett.* **1996**, *37*, 7053. (h) Takano, I.; Yasuda, I.; Nishijima, M.; Hitotsuyanagi, Y.; Takeya, K.; Itokawa, H. *Phytochemistry* **1997**, *44*, 735.

S0022-3263(97)01165-1 CCC: $14.00

Scheme 2



s) for **5** and between Me-15 (δ_H 1.71, d, J = 7.3 Hz) and H-2 (δ_H 5.50, s) for **6**. These data led to structures **5** and **6**.

The formation of compounds **4**−**6** could be explained by assuming two alternative paths. When the C(5)−N(9) bond of *N*-oxides **2** and **3** is cleaved[6] thermally (path a), a stable carbocation is formed, and attack of the oxygen anion produces compound **4**. When the Cope elimination[7] occurs (path b), the N(9)−C(10) bond is cleaved, and the reverse Cope reaction[8] in a regioisomeric fashion produces pentacyclic *N*-oxides, which undergo an elimination−addition reaction in a manner similar to path a, giving compounds **5** and **6**.

Table 1. Effect of Solvent on the Pyrolysis of 2[a]

	yield (%)[b]			
solvent[c]/products	**2**	**4**	**5**	**6**
MeOH	43	0	0	0
t-BuOH	72	5.4	3.6	0
TFE	83	0	0	0
MeCN	11	16	32	10
DCE	0	65	0	0
dioxane	0	47	40	8.0
THF	0	40	48	9.8
DME	0	38	49	10
	0	(37)[d]	(44)[d]	(7.7)[d]
toluene	0	48	43	10

[a] Each reaction was carried out in a sealed tube at 105 °C for 2 h. [b] HPLC yield. [c] TFE, 2,2,2-trifluoroethanol; DCE, 1,2-dichloroethane; dioxane, 1,4-dioxane; THF, tetrahydrofuran; DME, 1,2-dimethoxyethane. [d] Isolated yield.

Table 2. Effect of Solvent on the Pyrolysis of 3[a]

	yield (%)[b]			
solvent[c]/products	**3**	**4**	**5**	**6**
MeOH	91	0	0	0
t-BuOH	78	0	0	0
TFE	92	0	0	0
MeCN	69	0	0	0
DCE	0	58	0	0
dioxane	0	38	29	5.4
THF	0	33	35	7.6
DME	0	34	37	8.0
	0	(32)[d]	(36)[d]	(7.6)[d]
toluene	0	36	33	8.4

[a−d] See Table 1.

These thermal reactions are significantly influenced by the solvent used (Tables 1 and 2). Although the ether solvents (1,4-dioxane, tetrahydrofuran, 1,2-dimethoxyethane) and toluene gave compounds **4**−**6** in a similar ratio, 1,2-dichloroethane gave only compound **4**. In the case of the alcohol solvents (MeOH, *t*-BuOH, 2,2,2-trifluoroethanol) or slightly basic acetonitrile, the reaction did not occur or proceeded sluggishly.[9]

Zinc and acetic acid reduction of **5** and **6** gave ring-contracted homoharringtonine analogues **7** and **8** in yields of 96% and 67%, respectively. Their stereostructures were confirmed by the NOESY spectra.

Homoharringtonine (**1**) and the obtained analogues **2**−**8** were evaluated using P-388 leukemia cells, the IC_{50}

(6) A ready cleavage of the C(5)−N(9) bond for this type of skeleton has been reported: (a) Abraham, D. J.; Rosenstein, R. D.; McGandy, E. L. *Tetrahedron Lett.* **1969**, 4085. (b) Dolby, L. J.; Nelson, S. J.; Senkovich, D. *J. Org. Chem.* **1972**, *37*, 3691. (c) Schwab, J. M.; Parry, R. J.; Foxman, B. M. *J. Chem. Soc., Chem. Commun.* **1975**, 906. (d) Burkholder, T. P.; Fuchs, P. L. *J. Am. Chem. Soc.* **1990**, *112*, 9601. (e) Isono, N.; Mori, M. *J. Org. Chem.* **1995**, *60*, 115. (f) Lin, X.; Kavash, R. W.; Mariano, P. S. *J. Org. Chem.* **1996**, *61*, 7335.

(7) Cope, A. C.; Trumbull, E. R. *Org. React.* **1960**, *11*, 317.

(8) (a) House, H. O.; Manning, D. T.; Melillo, D. G.; Lee, L. F.; Haynes, O. R.; Wilkes, B. E. *J. Org. Chem.* **1976**, *41*, 855. (b) House, H. O.; Lee, L. F. *J. Org. Chem.* **1976**, *41*, 863. (c) Black, D. St. C.; Doyle, J. E. *Aust. J. Chem.* **1978**, *31*, 2317. (d) Oppolzer, W.; Siles, S.; Snowden, R. L.; Bakker, B. H.; Petrzilka, M. *Tetrahedron Lett.* **1979**, 4391. (e) Leeson, P. D.; James, K.; Baker, R. *J. Chem. Soc., Chem. Commun.* **1989**, 433. (f) Karady, S.; Corley, E. G.; Abramson, N. L.; Weinstock, L. M. *Tetrahedron Lett.* **1989**, *30*, 2191. (g) Gravestock, M. B.; Knight, D. W.; Thornton, S. R. *J. Chem. Soc., Chem. Commun.* **1993**, 169. (h) Fox, M. E.; Holmes, A. B.; Forbes, I. T.; Thompson, M. *J. Chem. Soc., Perkin Trans. 1* **1994**, 3379. (i) Oppolzer, W.; Spivey, A. C.; Bochet, C. G. *J. Am. Chem. Soc.* **1994**, *116*, 3139. (j) Davison, E. C.; Holmes, A. B.; Forbes, I. T. *Tetrahedron Lett.* **1995**, *36*, 9047. (k) Ciganek, E.; Read, J. M.; Calabrese, J. C. *J. Org. Chem.* **1995**, *60*, 5795. (l) Ciganek, E. *J. Org. Chem.* **1995**, *60*, 5803. (m) Coogan, M. P.; Knight, D. W. *Tetrahedron Lett.* **1996**, *37*, 6417.

(9) To the best of our knowledge, such thermal *N*-oxide skeletal rearrangements of alkaloids through Cope and reverse Cope reactions are unprecedented. To examine the generality of this unusual reaction, we attempted the thermal rearrangement of tetrahydroberberine *N*-oxides under the same conditions, but none of the rearranged products was obtained.

values being 0.017, 0.92, 1.9, 4.0, 15, 6.0, 6.2, and 1.5 μg/mL, respectively. Both *N*-oxides **2** and **3**, being regarded as the conformationally locked analogues of **1**, showed weaker activity compared with that of **1,** which has a nitrogen lone pair. Thus, the nitrogen lone pair on the cephalotaxine skeleton appears to be essential for its activity. Also, the weaker activity of analogues **4**−**8** compared with that of **1** is accounted for by the changes in the topology of the cephalotaxine skeleton through chemical modification.

Experimental Section

General. Analytical high performance liquid chromatography (HPLC) was carried out on a TSKgel silica 60 column (5 μm, 4.6 × 250 mm, TOSOH) at a flow rate of 1 mL/min. Semipreparative HPLC was carried out on a LiChrosorb Si 60 column (7 μm, 25 × 250 mm, Merck) at a flow rate of 7 mL/min. The effluent was monitored at 290 nm. Rotations were recorded in units of 10^{-1} deg cm^2 g^{-1}; ^{1}H and ^{13}C NMR spectra were collected using a 500 or 125 MHz instrument, respectively. Chemical shifts (δ) were reported in ppm. ^{1}H chemical shifts were calibrated using the tetramethylsilane resonance as internal standard. ^{13}C chemical shifts were referenced to the solvent ($CDCl_3$, 77.0 ppm). The chemical shift assignment was carried out by homonuclear correlation (COSY) and heteronuclear correlation (HMQC, HMBC) experiments. Mass spectroscopy was performed using EI and FAB ion sources.

Homoharringtonine *β*-*N*-oxide (2) and α-*N*-oxide (3). To a solution of homoharringtonine (**1**) (100 mg) in MeOH (0.5 mL) was added 30% aqueous H_2O_2 (0.1 mL), and the mixture was stirred at room temperature for 24 h. Methyl sulfide (50 μL) was added to the solution at 0 °C, and the mixture was stirred at room temperature for 3 h. The reaction mixture was concentrated under reduced pressure to give a residue, which was chromatographed (HPLC, SiO_2, 1:1:2 $CHCl_3$/*n*-hexane/MeOH) to provide *N*-oxides **2** (27 mg, 26%) and **3** (37 mg, 36%).

2: a colorless oil; $[\alpha]_D = -90°$ (*c* 0.22, MeOH); UV (MeOH) λ_{max} 292 nm (log ϵ 3.66); IR (film) 3350 br, 1742, 1652, 1505, 1490 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 1.16 (s, 3H), 1.18 (s, 3H), 1.23 (m, 1H), 1.38 (m, 2H), 1.40 (m, 1H), 1.50 (m, 2H), 1.71 (m, 1H), 1.86 (m, 1H), 2.25 (m, 1H), 2.29 (d, *J* = 16.5 Hz, 1H), 2.43 (d, *J* = 16.5 Hz, 1H), 2.74 (m, 1H), 2.99 (td, *J* = 10.0, 7.6 Hz, 1H), 3.06 (td, *J* = 10.0, 7.0 Hz, 1H), 3.37 (td, *J* = 10.0, 5.0 Hz, 1H), 3.54 (s, 3H), 3.64 (m, 2H), 3.73 (d, *J* = 8.4 Hz, 1H), 3.81 (s, 3H), 3.93 (m, 1H), 5.43 (s, 1H), 5.90 (d, *J* = 8.4 Hz, 1H), 5.94 (br s, 2H), 6.60 (s, 1H), 6.61 (s, 1H); Key NOESY correlations: H-1/H-6*β*, H-1/Me-19, H-3/H-4, H-4/H-6α, H-4/H-14, H-8α/H-11α, H-11α/H-17; ^{13}C NMR ($CDCl_3$) δ 17.7 (t), 19.3 (t), 28.8 (q), 29.7 (q), 30.3 (t), 38.3 (t), 39.4 (t), 42.7 (t), 43.5 (t), 51.5 (q), 55.8 (d), 57.9 (q), 62.5 (t), 66.6 (t), 70.4 (s) × 2, 75.9 (d), 89.3 (s), 101.3 (t), 101.6 (d), 109.3 (d), 112.1 (d), 125.8 (s), 130.7 (s), 146.7 (s), 147.9 (s), 160.7 (s), 170.3 (s), 173.8 (s); EIMS *m*/*z* (%) 561 (6, M$^+$), 545 (7), 530 (10), 314 (62), 298 (100); HRFABMS [M + H]$^+$ calcd for $C_{29}H_{40}NO_{10}$ 562.2652, found 562.2637.

3: a colorless oil; $[\alpha]_D = -179°$ (*c* 0.42, MeOH); UV (MeOH) λ_{max} 294 nm (log ϵ 3.54); IR (film) 3365 br, 1746, 1659, 1505, 1489 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 1.18 (s, 3H), 1.19 (s, 3H), 1.2−1.4 (m, 6H), 1.86 (d, *J* = 16.5 Hz, 1H), 1.89 (m, 1H), 1.97 (br t, *J* = 11.0 Hz, 1H), 2.22 (m, 1H), 2.27 (d, *J* = 16.5 Hz, 1H), 2.51 (dd, *J* = 14.7, 6.6 Hz, 1H), 2.94 (m, 1H), 3.45 (m, 1H), 3.61 (m, 3H), 3.61 (s, 3H), 3.74 (m, 1H), 3.75 (s, 3H), 3.94 (d, *J* = 9.7 Hz, 1H), 4.92 (s, 1H), 5.83 (br s, 1H), 5.86 (br s, 1H), 6.02 (d, *J* = 9.7 Hz, 1H), 6.51 (s, 1H), 6.64 (s, 1H); Key NOESY correlations: H-1/H-6*β*, H-1/H-10*β*, H-1/Me-19, H-3/H-4, H-4/H-6α, H-4/H-14, H-11α/H-17; ^{13}C NMR ($CDCl_3$) δ 17.7 (t), 18.3 (t), 28.6 (t), 29.0 (q), 29.4 (q), 38.9 (t), 39.4 (t), 42.3 (t), 43.6 (t), 51.6 (q), 52.1 (d), 58.0 (q), 62.6 (t), 70.7 (t), 70.7 (s), 72.8 (d), 74.7 (s), 84.9 (s), 100.0 (d), 100.7 (t), 109.2 (d), 111.5 (d), 128.5 (s), 130.4 (s), 145.7 (s), 145.9 (s), 161.7 (s), 170.6 (s), 173.6 (s); EIMS *m*/*z* (%) 561 (1, M$^+$), 545 (4), 530 (4), 314 (53), 298 (100); HRFABMS [M + H]$^+$ calcd for $C_{29}H_{40}NO_{10}$ 562.2652, found 562.2648.

Thermal Rearrangements of 2 and 3. A solution of **2** (100 mg) in 1,2-dimethoxyethane (1 mL) was heated at 105 °C in a sealed tube for 2 h. The mixture was concentrated under reduced pressure to give a residue, which was chromatographed (HPLC, SiO_2, 2:2:1 $CHCl_3$/*n*-hexane/MeOH) to afford compounds **4** (37 mg, 37%), **5** (44 mg, 44%), and **6** (7.7 mg, 7.7%). In the same manner, compound **3** (100 mg) gave **4** (32 mg, 32%), **5** (36 mg, 36%), and **6** (7.6 mg, 7.6%).

1-[(1*R*,4*S*,5*S*)-3-Methoxy-9,11,21-trioxa-17-azapentacyclo-[15.3.1.0^{1,5}.0^{6,14}.0^{8,12}]henicosa-2,6,8(12),13-tetraen-4-yl] 4-methyl (2*R*)-2-hydroxy-2-(4-hydroxy-4-methylpentyl)succinate (4): a colorless oil; $[\alpha]_D = -209°$ (*c* 0.55, MeOH); UV (MeOH) λ_{max} 292 nm (log ϵ 3.70); IR (film) 3516 br, 1743, 1648, 1507, 1490 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 1.16 (s, 3H), 1.17 (s, 3H), 1.37 (m, 2H), 1.44 (m, 2H), 1.56 (m, 1H), 1.68 (m, 2H), 1.79 (m, 2H), 2.04 (td, *J* = 12.8, 6.0 Hz, 1H), 2.46 (ddd, *J* = 14.0, 12.8, 2.0 Hz, 1H), 2.54 (d, *J* = 16.5 Hz, 1H), 2.56 (ddd, *J* = 13.5, 10.8, 4.0 Hz, 1H), 2.70 (br dd, *J* = 17.5, 9.0 Hz, 1H), 2.77 (d, *J* = 16.5 Hz, 1H), 2.84 (ddd, *J* = 13.5, 10.8, 2.0 Hz, 1H), 2.89 (m, 1H), 3.32 (d, *J* = 7.2 Hz, 1H), 3.45 (s, 3H), 3.64 (m, 1H), 3.65 (s, 3H), 4.97 (s, 1H), 5.78 (d, *J* = 7.2 Hz, 1H), 5.89 (d, *J* = 1.5 Hz, 1H), 5.90 (d, *J* = 1.5 Hz, 1H), 6.59 (s, 1H), 6.66 (s, 1H); Key NOESY correlations: H-2/OMe-3, H-2/H-19*β*, H-2/H-20*β*, H-4/H-5, H-5/H-7, H-5/H-20α, H-13/H-15α; ^{13}C NMR ($CDCl_3$) δ 17.8 (t), 19.5 (t), 29.0 (q), 29.3 (q), 29.7 (t), 35.6 (t), 39.3 (t), 43.0 (t), 43.8 (t), 49.4 (t), 51.4 (q), 55.5 (t), 57.1 (q), 59.2 (d), 70.8 (s), 74.7 (s), 77.5 (d), 87.5 (s), 101.0 (t), 102.8 (d), 111.7 (d), 114.4 (d), 129.4 (s), 134.7 (s), 145.3 (s), 146.3 (s), 161.4 (s), 170.2 (s), 174.7 (s); EIMS *m*/*z* (%) 561 (15, M$^+$), 545 (13), 530 (6), 314 (100), 298 (72); HRFABMS [M + H]$^+$ calcd for $C_{29}H_{40}NO_{10}$ 562.2652, found 562.2650.

1-[(1*R*,4*S*,5*S*,15*S*)-3-Methoxy-15-methyl-9,11,20-trioxa-16-azapentacyclo[14.3.1.0^{1,5}.0^{6,14}.0^{8,12}]icosa-2,6,8(12),13-tetraen-4-yl] 4-methyl (2*R*)-2-hydroxy-2-(4-hydroxy-4-methylpentyl)-succinate (5): an amorphous solid; $[\alpha]_D = -148°$ (*c* 1.00, MeOH); UV (MeOH) λ_{max} 292 nm (log ϵ 3.62); IR (film) 3210 br, 1744, 1656, 1489 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 1.15 (s, 3H), 1.18 (m, 1H), 1.18 (s, 3H), 1.3−1.45 (m, 5H), 1.56 (m, 1H), 1.83 (d, *J* = 6.8 Hz, 3H), 1.85 (d, *J* = 16.4 Hz, 1H), 1.88 (ddd, *J* = 13.0, 7.5, 5.0 Hz, 1H), 2.27 (m, 1H), 2.29 (d, *J* = 16.4 Hz, 1H), 2.80 (dt, *J* = 13.0, 8.3 Hz, 1H), 3.01 (ddd, *J* = 11.5, 8.9, 7.0 Hz, 1H), 3.24 (ddd, *J* = 11.5, 8.1, 5.8 Hz, 1H), 3.60 (d, *J* = 8.1 Hz, 1H), 3.60 (s, 3H), 3.79 (s, 3H), 4.39 (q, *J* = 6.8 Hz, 1H), 5.29 (s, 1H), 5.91 (d, *J* = 8.1 Hz, 1H), 5.96 (d, *J* = 1.4 Hz, 1H), 5.99 (d, *J* = 1.4 Hz, 1H), 6.62 (s, 1H), 6.83 (br s, 1H); Key NOESY correlations: H-2/OMe-3, H-2/H-15, H-2/H-19*β*, H-4/H-5, H-5/H-7, H-5/H-19α, H-13/Me-15, Me-15/H-17α, Me-15/H-17*β*, H-15/H-17*β*; ^{13}C NMR ($CDCl_3$) δ 12.2 (q), 17.6 (t), 21.9 (t), 28.7 (q), 29.8 (q), 37.9 (t), 39.4 (t), 42.8 (t), 43.6 (t), 51.6 (q), 51.7 (d), 58.0 (q), 62.5 (t), 65.3 (d), 70.2 (s), 74.5 (s), 76.2 (d), 89.0 (s), 101.5 (t), 102.5 (d), 106.2 (d), 109.7 (d), 125.4 (s), 130.2 (s), 147.7 (s), 147.8 (s), 160.1 (s), 170.2 (s), 173.5 (s); EIMS *m*/*z* (%) 561 (1, M$^+$), 543 (2), 530 (18), 314 (18), 298 (100); HRFABMS [M + H]$^+$ calcd for $C_{29}H_{40}NO_{10}$ 562.2652, found 562.2669.

1-[(1*R*,4*S*,5*S*,15*R*)-3-Methoxy-15-methyl-9,11,20-trioxa-16-azapentacyclo[14.3.1.0^{1,5}.0^{6,14}.0^{8,12}]icosa-2,6,8(12),13-tetraen-4-yl] 4-methyl (2*R*)-2-hydroxy-2-(4-hydroxy-4-methylpentyl)succinate (6): a colorless oil; $[\alpha]_D = -141°$ (*c* 0.20, MeOH); UV (MeOH) λ_{max} 292 nm (log ϵ 3.62); IR (film) 3360 br, 1744, 1661, 1488 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 1.16 (s, 3H), 1.17 (s, 3H), 1.18 (m, 1H), 1.32 (m, 2H), 1.35 (m, 1H), 1.44 (m, 2H), 1.71 (d, *J* = 7.3 Hz, 3H), 1.71 (m, 1H), 1.82 (m, 1H), 1.92 (d, *J* = 16.0 Hz, 1H), 2.30 (m, 1H), 2.33 (d, *J* = 16.0 Hz, 1H), 2.96 (dt, *J* = 12.5, 9.2 Hz, 1H), 3.51 (m, 1H), 3.63 (ddd, *J* = 11.5, 10.0, 6.1 Hz, 1H), 3.68 (s, 3H), 3.72 (s, 3H), 3.78 (d, *J* = 8.9 Hz, 1H), 4.39 (q, *J* = 7.3 Hz, 1H), 5.50 (s, 1H), 5.91 (d, *J* = 1.3 Hz, 1H), 5.97 (d, *J* = 1.3 Hz, 1H), 6.12 (d, *J* = 8.9 Hz, 1H), 6.54 (s, 1H), 6.59 (s, 1H); Key NOESY correlations: H-2/OMe-3, H-2/Me-15, H-2/H-19*β*, H-4/H-5, H-5/H-7, H-5/H-19α, H-13/H-15, H-15/H-17α, H-15/H-17*β*; ^{13}C NMR ($CDCl_3$) δ 17.7 (t), 18.4 (q), 20.7 (t), 29.2 (q), 29.3 (q), 39.1 (t), 40.6 (t), 42.8 (t), 43.7 (t), 50.4 (d), 51.8 (q), 58.0 (q), 70.7 (s), 71.5 (d), 72.0 (t), 74.7 (s), 76.8 (d), 84.7 (s), 101.4 (t), 104.5 (d), 107.9 (d), 110.2 (d), 122.1 (s), 131.0 (s), 147.4 (s) × 2, 156.6 (s), 170.4 (s), 173.8 (s); EIMS *m*/*z* (%) 530 (20), 314 (35), 300 (100), 298 (95); HRFABMS [M + H]$^+$ calcd for $C_{29}H_{40}NO_{10}$ 562.2652, found: 562.2667.

Reduction of 4 to Homoharringtonine (1). To a solution of **4** (20 mg) in AcOH (1 mL) was added zinc powder (20 mg), and the mixture was stirred at 47 °C for 1 h. The reaction mixture was filtrated and concentrated. The residue was dissolved in $CHCl_3$ (35 mL) and washed successively with saturated aqueous $NaHCO_3$ (5 mL) and brine (5 mL). The

organic layer was dried over Na_2SO_4 and filtered and the solvent removed in vacuo. The residue was chromatographed (SiO_2, 9:1 $CHCl_3$/MeOH) to provide homoharringtonine (**1**) (18 mg, 94%).

1-[(1*S*,3a*R*,8*S*,13b*S*)-2-Methoxy-8-methyl-5,6,8,13b-tetrahydro-1*H*,4*H*-cyclopenta[*c*][1,3]dioxolo[4,5-*g*]pyrrolo-[1,2-*b*]isoquinolin-1-yl] 4-Methyl (2*R*)-2-Hydroxy-2-(4-hydroxy-4-methylpentyl)succinate (7). Compound **7** was obtained in 96% yield from **5** by the same procedure described for the reduction of **4**: a colorless oil; $[\alpha]_D = -232^\circ$ (*c* 0.55, MeOH); UV (MeOH) λ_{max} 292 nm (log ϵ 3.68); IR (film) 3500 br, 1745, 1658, 1504, 1485 cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.14 (m, 1H), 1.17 (s, 6H), 1.36 (m, 2H), 1.42 (m, 2H), 1.44 (m, 2H), 1.49 (d, J = 7.0 Hz, 3H), 1.70 (m, 1H), 1.75 (m, 1H), 1.82 (d, J = 16.2 Hz, 1H), 2.10 (br dd, J = 15.0, 8.0 Hz, 1H), 2.17 (m, 1H), 2.22 (d, J = 16.2 Hz, 1H), 2.81 (dt, J = 9.5, 6.5 Hz, 1H), 3.34 (d, J = 8.6 Hz, 1H), 3.61 (s, 3H), 3.67 (s, 3H), 3.89 (q, J = 7.0 Hz, 1H), 4.78 (s, 1H), 5.88 (d, J = 1.5 Hz, 1H), 5.89 (d, J = 8.6 Hz, 1H), 5.92 (d, J = 1.5 Hz, 1H), 6.54 (s, 1H), 6.78 (s, 1H); Key NOESY correlations: H-1/H-13b, OMe-2/H-3, H-3/H-4β, H-4α/H-13b, H-6β/Me-8, H-6β/ H-8, Me-8/ H-9, H-13/H-13b; ^{13}C NMR ($CDCl_3$) δ 17.5 (t), 17.9 (q), 23.3 (t), 29.0 (q), 29.2 (q), 39.1 (t), 40.8 (t), 42.6 (t), 43.7 (t), 45.7 (t), 48.7 (d), 49.3 (d), 51.6 (q), 57.4 (q), 70.8 (s), 72.8 (s), 74.5 (s), 76.6 (d), 100.7 (t), 106.1 (d), 106.6 (d), 110.5 (d), 127.0 (s), 135.2 (s), 145.7 (s), 146.3 (s), 158.0 (s), 170.3 (s), 173.8 (s); EIMS *m*/*z* (%) 545 (2, M^+), 530 (85), 512 (12), 502 (10), 298 (100); HRFABMS $[M + H]^+$ calcd for $C_{29}H_{40}NO_9$ 546.2703, found 546.2727.

1-[(1*S*,3a*R*,8*R*,13b*S*)-2-Methoxy-8-methyl-5,6,8,13b-tetrahydro-1*H*,4*H*-cyclopenta[*c*][1,3]dioxolo[4,5-*g*]pyrrolo-[1,2-*b*]isoquinolin-1-yl] 4-Methyl (2*R*)-2-Hydroxy-2-(4-hydroxy-4-methylpentyl)succinate (8). Compound **8** was obtained in 67% yield from **6** by the same procedure described for the reduction of **4**: a colorless oil; $[\alpha]_D = -218^\circ$ (*c* 0.10, MeOH); UV (MeOH) λ_{max} 292 nm (log ϵ 3.65); IR (film) 3500 br, 1743, 1663, 1484 cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.15−1.45 (m, 6H), 1.15 (s, 3H), 1.16 (s, 3H), 1.39 (d, J = 7.4 Hz, 3H), 1.60 (m, 1H), 1.79 (m, 1H), 1.81 (m, 1H), 1.87 (d, J = 16.2 Hz, 1H), 2.18 (m, 1H), 2.25 (d, J = 16.2 Hz, 1H), 2.50 (br dd, J = 16.0, 8.5 Hz, 1H), 3.10 (m, 1H), 3.51 (d, J = 8.9 Hz, 1H), 3.62 (s, 3H), 3.67 (s, 3H), 3.94 (q, J = 7.4 Hz, 1H), 4.88 (s, 1H), 5.83 (d, J = 1.5 Hz, 1H), 5.92 (d, J = 1.5 Hz, 1H), 6.07 (d, J = 8.9 Hz, 1H), 6.49 (s, 1H), 6.59 (s, 1H); Key NOESY correlations: H-1/H-13b, OMe-2/H-3, H-3/H-4β, H-3/Me-8, H-4α/H-13b, H-6α/H-8, H-6β/H-8, H-8/H-9, H-13/H-13b; ^{13}C NMR ($CDCl_3$) δ 17.8 (t), 23.1 (t), 23.8 (q), 29.0 (q), 29.2 (q), 38.9 (t), 42.9 (t), 43.8 (t), 44.5 (t), 47.3 (d), 51.7 (q), 55.3 (t), 57.3 (q), 58.0 (d), 69.5 (s), 70.8 (s), 74.6 (s), 76.9 (d), 100.7 (t), 107.8 (d), 110.6 (d), 110.9 (d), 124.2 (s), 133.9 (s), 145.8 (s), 146.1 (s), 154.2 (s), 170.4 (s), 174.0 (s); EIMS *m*/*z* (%) 545 (1, M^+), 530 (100), 512 (23), 456 (8), 298 (46); HREIMS $[M - CH_3]^+$ calcd for $C_{28}H_{36}NO_9$ 530.2390, found 530.2374.

Acknowledgment. The authers gratefully thank Mr. Akihiro Shibata (Jasco. Co.) for high-resolution FABMS measurements.

Supporting Information Available: Full ^1H and ^{13}C NMR chemical shifts assignments and 500 MHz ^1H NMR spectra of compounds **2**−**8** (13 pages). This material is contained in libraries on microfiche, immediately follows this article in the microfilm version of the journal, and can be ordered from the ACS; see any current masthead page for ordering information.

JO9711652